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Letter to the Editor

Another Observation of Atypical Radiologic Findings in Achondroplasia Not Due to a Common Mutation of the FGFR-3 Gene: Reply to Dr. Gorlin

To the Editor:

We are grateful for Dr. Gorlin's comment on our report "Atypical Radiological Findings in Achondroplasia With Uncommon Mutation of the Fibroblast Growth Factor Receptor-3 (FGFR-3) Gene (Gly to Cys Transition at Codon 375)" [Nishimura et al., 1995]. Dr. Gorlin postulates that the atypical skeletal changes of the achondroplastic child (a 10-year-old boy) described in our report, including decrease in the height of the vertebral bodies to a greater extent than usual and exceptionally severe metaphyseal dysplasia, might not have been due to the uncommon mutation of the FGFR-3 gene (Gly375Cys) that he harbored, but rather signified a genetic combination of achondroplasia with an unknown bone disease that might have been transmitted from his father, who was described as short. As presented in the report, it was not possible to examine the father, and we are unable to address Dr. Gorlin's concern directly. However, we would like to present another case of atypical skeletal changes in an achondroplastic child who did not carry the common mutation of the FGFR-3 gene (Gly380Arg) [Shiang et al., 1994]. This additional example would suggest that uncommon mutations of the FGFR-3 gene may cause atypical skeletal changes in achondroplasia.

The patient was a Japanese boy and the second child of healthy, unrelated parents: a 38-year-old father and a 33-year-old mother. The family history was unremarkable except for sudden death of unknown cause of an elder brother of the patient at age 2 weeks. The patient was found to have short femora at 35 weeks of gestation on fetal ultrasonography, but was delivered normally at term. Birth length was 46.0 cm (–2.0 SD), weight 2,986 g (–0.5 SD), and OFC 33.0 cm (–0.4 SD). The face appeared unremarkable. Although mild micromelia was suspected, radiographic examination was not carried out at this time. Thereafter, rhizomelia became evident, and trident hands were noted. A skeletal survey at age 6 months disclosed radiologic changes consistent with those in achondroplasia, including nar-

Fig. 1. Radiologic findings consistent with achondroplasia, including interpediculate narrowing of the lumbar spine, hypoplastic ilia, and radiolucencies of the proximal femora.

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Figs. 2 and 3. Milder metaphyseal cupping and modification of the vertebral bodies.

row thorax, some modification of the vertebral bodies, interpediculate narrowing of the lumbar spine, hypoplastic ilia, and short limbs with mild metaphyseal cupping (Fig. 1).

However, overall the skeletal abnormalities were milder than those in typical achondroplasia, particularly with regard to spondylar deformity and metaphyseal cupping (Figs. 2, 3). Other than macrocephaly, his craniofacial structure was considered normal. At age 8 months, length was 65.4 cm (50–75th centile of Japanese achondroplastic individuals), weight 7,730 g (−1.1 SD of the general population), and OFC 47.2 cm (+1.9 SD of the general population). SSCP analysis of the PCR fragments of the FGFR-3 gene transmembrane domain did not show abnormal bands related to the common mutation of FGFR-3 gene (Gly380Arg) and to an uncommon mutation (Gly375Cys) causing achondroplastic individuals [Superti-Furga et al., 1995; Ikegawa et al., 1995]. At age 1$\frac{7}{12}$ years, height was 71.4 cm (50–75th centile of Japanese achondroplastic individuals), weight 9,890 g (−0.8 SD of the general population), and OFC 50.0 g (+1.4 SD of the general population). Skeletal survey yielded the same findings as those on the previous examination, other than the development of posterior scalloping of the lumbar vertebral bodies. His facial appearance was not typical of achondroplasia: he had neither frontal bossing nor overt midface "recession."

The clinical and radiologic manifestations in the present patient, particularly the normal facial structure

and milder metaphyseal modification, were not characteristic of achondroplasia, which provoked some confusion in clinical diagnosis. In addition, molecular examination failed to demonstrate known mutations of the FGFR-3 gene in achondroplasia [Bonaventure et al., 1996]. Nevertheless, the present patient has achondroplasia because of qualitative and quantitative similarities to "typical achondroplasia" in radiologic findings and dissimilarities to the other disorders in the "achondroplasia family" proposed by Spranger [1988]. In general, achondroplastic individuals exhibit very little, if any, phenotypic variability, and "atypical achondroplasia" is extremely rare, as is heterogeneity of mutation of the FGFR-3 gene (Gly380Arg) in achondroplasia. However, the present patient warrants that achondroplasia include, in part, unusual phenotypic variants. Moreover, interfamilial variability in achondroplasia is postulated by the fact that the standard deviation in the growth curve is larger in this disorder than in the general population [Rimoin, 1988]. Therefore, further investigation of phenotype-genotype correlation in achondroplasia is required not only to elucidate these issues, but also to preclude the diagnostic confusion exemplified in the present patient.

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